Drug Class Review
on
ACE Inhibitors

Update #3: Preliminary Scan Report

February 2007

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update

June 2005 (searches through February 2005)

Scope and Key Questions

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

Key Questions

1. For adult patients with essential hypertension, heart failure, high cardiovascular risk factors, diabetic nephropathy, nondiabetic nephropathy, or recent myocardial infarction, do angiotensin converting enzyme (ACE) inhibitors differ in effectiveness?

2. For adult patients with essential hypertension, heart failure, high cardiovascular risk factors, diabetic nephropathy, nondiabetic nephropathy, or recent myocardial infarction, do ACE inhibitors differ in safety or adverse events?

3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one ACE inhibitor is more effective or associated with fewer adverse events?

Inclusion Criteria

Populations

Adult patients with any of the following indications:

- Hypertension without compelling indications. This refers to patients with hypertension who do not have any of the following indications:
    a. a history of coronary heart disease (CHD)

b. other cardiovascular diseases (CVD), such as cerebrovascular (carotid) disease, peripheral vascular disease, or a history of stroke
c. other risk factors for CAD/CVD, such as diabetes, smoking or hyperlipidemia
d. renal insufficiency

- Hypertension with compelling indications. This refers to patients with hypertension who also have one of the conditions listed above.
- High cardiovascular risk. This group includes patients who have a history of CHD/CVD, or a combination of other risk factors for CHD/CVD, such as diabetes, smoking, and hyperlipidemia. These patients may or may not have hypertension as well.
- Recent myocardial infarction. This group includes patients who have had a recent myocardial infarction and who have normal left ventricular function or asymptomatic left ventricular dysfunction.
- Heart failure. This group includes patients who have symptomatic heart failure due to left ventricular systolic dysfunction, with or without hypertension.
- Diabetic nephropathy. This group includes patients with Type 1 or Type 2 diabetes who have laboratory evidence of nephropathy, such as albuminuria or decreased creatinine clearance.

Interventions

- benazepril
- captopril
- cilazapril
- enalapril
- fosinopril
- lisinopril
- moexipril
- quinapril
- ramipril
- perindopril
- trandolapril

Effectiveness outcomes

Effectiveness measures varied according to the clinical condition:

Hypertension

- All-cause and cardiovascular mortality
- Cardiovascular events (stroke, myocardial infarction, or development of heart failure)
- End-stage renal disease (including dialysis or need for transplantation) or clinically significant and permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance)
- Quality-of-life

(Trials that focused on blood pressure reduction but not on any health outcomes were excluded from the effectiveness review)

High cardiovascular risk

- All-cause and cardiovascular mortality
- Cardiovascular events (stroke, myocardial infarction, or development of heart failure)

Recent myocardial infarction

- All-cause and cardiovascular mortality
- Cardiovascular events (usually, development of heart failure)

Heart failure

- All-cause or cardiovascular mortality
- Symptomatic improvement (heart failure class, functional status, visual analogue scores)
- Hospitalizations for heart failure

Diabetic nephropathy/non-diabetic nephropathy

- End-stage renal disease (including dialysis or need for transplantation)
- Clinically significant and permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance)

Safety outcomes

- Withdrawals
- Withdrawals due to adverse effects
- Specific adverse effects or withdrawals due to specific adverse events, for example, symptomatic hypotension

Study designs

1. Randomized controlled trials that compared one of the included ACE inhibitors to another.
2. Systematic reviews of the clinical effectiveness or adverse event rates of ACE inhibitors for included clinical conditions that reported an included outcome.
3. Large (> 100 patients) placebo-controlled trials for included clinical conditions that reported an included outcome.
4. Randomized controlled trials and large, good-quality observational studies that evaluated adverse event rates for one or more of the included ACE Inhibitors.

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE, Ovid MEDLINE Daily Update, and Ovid MEDLINE In-Process & Other Non-Indexed Citations from January 2005 through January Week 1, 2007 using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (http://www.fda.gov/medwatch/safety.htm) and Health Canada (http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/index_e.html) websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

Searches resulted in 218 citations. Of those, there are 23 new potentially relevant trials (see Appendix A, attached).

New Drugs/Indications

No new ACE Inhibitors were identified.

There is a new indication for perindopril in patients with stable coronary artery disease to reduce the risk of cardiovascular mortality or non-fatal myocardial infarction.

New Safety Alerts

The FDA issued a safety alert in June 2006 for the ACE Inhibitors drug class regarding increased risk of major congenital malformations in infants whose mothers had taken an ACE inhibitor during the first trimester of pregnancy. At this time, based on this one observational study, the FDA does not plan to change the pregnancy categories for ACE inhibitors. The full text of the warning is available at:
http://www.fda.gov/cder/drug/infopage/ace_inhibitors/default.htm.

Several new precautions and warnings have been added to the lisinopril product label:
1) Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) occurring in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy.
2) Diabetic patients treated with oral antidiabetic agents or insulin starting an ACE inhibitor should be told to closely monitor for hypoglycemia, especially during the first month of combined use.
3) Eplerenone has been added under the Agents Increasing Serum Potassium subsection.
4) Head and Neck Angioedema subsection revised:
Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient. Very rarely, fatalities have been reported due to angioedema associated with laryngeal edema or tongue edema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery.
5) Hepatic Failure subsection revised:
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant hepatic necrosis, and (sometimes) death.

Appendix A. Abstracts of potentially relevant new trials of ACE Inhibitors

Arima, H., R. G. Hart, et al. (2005). "Perindopril-based blood pressure-lowering reduces major vascular events in patients with atrial fibrillation and prior stroke or transient ischemic attack." Stroke **36**(10): 2164-9.

BACKGROUND AND PURPOSE: Patients with atrial fibrillation have a high risk of stroke and other vascular events even if anticoagulated. The primary objective here is to determine whether routine blood pressure-lowering provides additional protection for this high-risk patient group. METHODS: This study was a subsidiary analysis of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS)--a randomized, placebo-controlled trial that established the beneficial effects of blood pressure--lowering in a heterogeneous group of patients with cerebrovascular disease. A total of 6105 patients were randomly assigned to either active treatment (2 to 4 mg perindopril for all participants plus 2.0 to 2.5 mg indapamide for those without an indication for or a contraindication to a diuretic) or matching placebo(s). Outcomes are total major vascular events, cause-specific vascular outcomes, and death from any cause. RESULTS: There were 476 patients with atrial fibrillation at baseline, of whom 51% were taking anticoagulants. In these patients, active treatment lowered mean blood pressure by 7.3/3.4 mm Hg and was associated with a 38% (95% confidence interval [CI], 6 to 59) reduction in major vascular events and 34% (95% CI, -13 to 61) reduction in stroke. The benefits of blood pressure-lowering in patients with atrial fibrillation were achieved irrespective of the use of anticoagulant therapy (P homogeneity=0.8) or the presence of hypertension (P homogeneity=0.4). CONCLUSIONS: For most patients with atrial fibrillation, routine blood pressure-lowering is likely to provide protection against major vascular events additional to that conferred by anticoagulation.

Arnett, D. K., B. R. Davis, et al. (2005). "Pharmacogenetic association of the angiotensin-converting enzyme insertion/deletion polymorphism on blood pressure and cardiovascular risk in relation to antihypertensive treatment: the Genetics of Hypertension-Associated Treatment (GenHAT) study." Circulation **111**(25): 3374-83.

BACKGROUND: Previous studies have reported that blood pressure response to antihypertensive medications is influenced by genetic variation in the renin-angiotensin-aldosterone system, but no clinical trails have tested whether the ACE insertion/deletion (I/D) polymorphism modifies the association between the type of medication and multiple cardiovascular and renal phenotypes. METHODS AND RESULTS: We used a double-blind, active-controlled randomized trial of antihypertensive treatment that included hypertensives > or =55 years of age with > or =1 risk factor for cardiovascular disease. ACE I/D genotypes were determined in 37 939 participants randomized to chlorthalidone, amlodipine, lisinopril, or doxazosin treatments and followed up for 4 to 8 years. Primary outcomes included fatal coronary heart disease (CHD) and/or nonfatal myocardial infarction. Secondary outcomes included stroke, all-cause mortality, combined CHD, and combined cardiovascular disease. Fatal and nonfatal CHD occurred in 3096 individuals during follow-up. The hazard rates for fatal and nonfatal CHD and the secondary outcomes were similar across antihypertensive treatments. ACE I/D genotype group was not associated with fatal and nonfatal CHD (relative risk of DD versus ID and II, 0.99; 95% CI, 0.91 to 1.07) or any secondary outcome. The 6-year

hazard rate for fatal and nonfatal CHD in the DD genotype group was not statistically different from the ID and II genotype group by type of treatment. No secondary outcome measure was statistically different across antihypertensive treatment and ACE I/D genotype strata. CONCLUSIONS: ACE I/D genotype group was not a predictor of CHD, nor did it modify the response to antihypertensive treatment. We conclude that the ACE I/D polymorphism is not a useful marker to predict antihypertensive treatment response.

Bosch, J., E. Lonn, et al. (2005). "Long-term effects of ramipril on cardiovascular events and on diabetes: results of the HOPE study extension." Circulation **112**(9): 1339-46.

BACKGROUND: We have previously demonstrated that ramipril reduces vascular events and new diagnoses of diabetes when given for a 4.5-year period. However, it is not known whether the benefits are observed in subgroups of patients at varying risk or on other proven therapies and whether the benefits are sustained beyond the current trial. The 2 aims of this investigation were to assess whether the benefits observed during the HOPE trial were (1) maintained after trial cessation during an additional 2.6 years of follow-up and (2) observed in subgroups based on risk and ancillary treatments. METHODS AND RESULTS: Of the initial 267 study centers and 9297 patients, 174 centers and 4528 patients agreed to further follow-up. The rates of use of angiotensin-converting-enzyme inhibitors (ACEIs) in the 2 groups (72% ramipril versus 68% placebo) were similar after the end of the trial. During the posttrial follow-up, patients allocated to ramipril had a 19% further lower relative risk (RR) of myocardial infarction (95% confidence interval [CI], 0.65 to 1.01), a 16% lower RR (95% CI, 0.70 to 0.99) of revascularization, and a 34% lower RR of a new diagnosis of diabetes (95% CI, 0.46 to 0.95). Similar RR reductions in vascular events were observed during and after the active phase of the trial, regardless of baseline risk (RR of 0.76, 0.89, and 0.83 for low-, medium-, and high-risk patients, respectively) or ancillary treatments (RR of 0.90 for aspirin, 0.76 for beta-blockers, and 0.84 for lipid-lowering medication). CONCLUSIONS: The benefits of ramipril observed during the active period of the HOPE trial were maintained during posttrial follow-up for cardiovascular death, stroke, and hospitalization for heart failure. Additional reductions in myocardial infarction, revascularization, and the development of diabetes were observed during the follow-up phase despite similar rates of ACEI use in the 2 randomized groups. These benefits were consistent regardless of patient risk or ancillary treatments.

Contreras, G., T. Greene, et al. (2005). "Blood pressure control, drug therapy, and kidney disease." Hypertension **46**(1): 44-50.

The African American Study of Kidney Disease and Hypertension examined the effect on renal function decline of 2 blood pressure (BP) goals (low mean arterial pressure [MAP] < or =92 versus usual MAP 102 to 107 mm Hg) and 3 antihypertensives (ramipril versus amlodipine versus metoprolol). We previously reported that in all drug groups combined the BP intervention had similar effects on the primary outcome of glomerular filtration rate (GFR) slope or the main secondary clinical composite outcome of end-stage renal disease (ESRD), death, or GFR decline by 50% or 25 mL/min per 1.73 m2. This report examines the effect of the BP intervention separately in the 3 drug groups. The BP effect was similar among the drug groups for either GFR slope or the main clinical composite. However, the BP effect differed significantly among the drug groups for the composite of ESRD or death (P=0.035) and ESRD alone (P=0.021). Higher event rates for amlodipine

patients assigned to the usual BP goal (0.087 per patient-year for ESRD or death and 0.064 per patient-year for ESRD) were seen compared with the remaining groups of the factorial design (range, 0.041 to 0.050 for ESRD or death; and range, 0.027 to 0.036 for ESRD). The low BP goal was associated with reduced risk of ESRD or death (risk reduction 51%; 95% confidence interval, 13% to 73%) and ESRD (54%; 8% to 77%) for amlodipine patients, but not for patients assigned to the other drug groups. These secondary analyses suggest a benefit of the low BP goal among patients assigned to amlodipine, but they must be interpreted cautiously.

Daly, C. A., K. M. Fox, et al. (2005). "The effect of perindopril on cardiovascular morbidity and mortality in patients with diabetes in the EUROPA study: results from the PERSUADE substudy.[see comment]." European Heart Journal **26**(14): 1369-78.

AIMS: The aim of this study was to assess the effect of the angiotensin converting enzyme inhibitor perindopril on cardiovascular events in diabetic patients with coronary artery disease. METHODS AND RESULTS: A total of 1502 diabetic patients with known coronary artery disease and without heart failure of 12 218 overall in the EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery (EUROPA) disease were randomized in a double-blinded manner to perindopril 8 mg once daily or placebo. Follow-up was for a median of 4.3 years. The primary end point was cardiovascular death, non-fatal myocardial infarction, and resuscitated cardiac arrest. Perindopril treatment was associated with a non-significant reduction in the primary endpoint in the diabetic population, 12.6 vs. 15.5%, relative risk reduction 19% [(95% CI, -7 to 38%), P=0.13]. This was of similar relative magnitude to the 20% risk reduction observed in the main EUROPA population. CONCLUSION: Perindopril tends to reduce major cardiovascular events in diabetic patients with coronary disease in addition to other preventive treatments and the trend towards reduction was of a similar relative magnitude to that observed the general population with coronary artery disease.

Davis, B. R., L. B. Piller, et al. (2006). "Role of diuretics in the prevention of heart failure: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.[see comment]." Circulation **113**(18): 2201-10.

BACKGROUND: Hypertension is a major cause of heart failure (HF) and is antecedent in 91% of cases. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) stipulated assessment of the relative effect of chlorthalidone, lisinopril, and amlodipine in preventing HF. METHODS AND RESULTS: ALLHAT was a double-blind, randomized, clinical trial in 33,357 high-risk hypertensive patients aged > or =55 years. Hospitalized/fatal HF outcomes were examined with proportional-hazards models. Relative risks (95% confidence intervals; P values) of amlodipine or lisinopril versus chlorthalidone were 1.35 (1.21 to 1.50; <0.001) and 1.11 (0.99 to 1.24; 0.09). The proportional hazards assumption of constant relative risk over time was not valid. A more appropriate model showed relative risks of amlodipine or lisinopril versus chlorthalidone during year 1 were 2.22 (1.69 to 2.91; <0.001) and 2.08 (1.58 to 2.74; <0.001), and after year 1, 1.22 (1.08 to 1.38; P=0.001) and 0.96 (0.85 to 1.10; 0.58). There was no significant interaction between prior medication use and treatment. Baseline blood pressures were equivalent (146/84 mm Hg) and at year 1 were 137/79, 139/79, and 140/80 mm Hg in those given chlorthalidone, amlodipine, and lisinopril. At 1 year, use of added open-label atenolol, diuretics, angiotensin-converting enzyme

inhibitors, and calcium channel blockers in the treatment groups was similar. CONCLUSIONS: HF risk decreased with chlorthalidone versus amlodipine or lisinopril use during year 1. Subsequently, risk for those individuals taking chlorthalidone versus amlodipine remained decreased but less so, whereas it was equivalent to those given lisinopril. Prior medication use, follow-up blood pressures, and concomitant medications are unlikely to explain most of the HF differences. Diuretics are superior to calcium channel blockers and, at least in the short term, angiotensin-converting enzyme inhibitors in preventing HF in hypertensive individuals.

Deckers, J. W., D. M. Goedhart, et al. (2006). "Treatment benefit by perindopril in patients with stable coronary artery disease at different levels of risk." European Heart Journal **27**(7): 796-801.

AIMS: Patients with stable coronary artery disease (CAD) are at increased risk. Estimation of individual risk is difficult. We developed a cardiovascular risk model based on the EUROPA study population and investigated whether benefit of long-term administration of the angiotensin-converting enzyme (ACE)-inhibitor perindopril was modified by risk level. METHODS AND RESULTS: A total of 12 218 patients with stable CAD were treated with 8 mg perindopril or placebo. Baseline patient characteristics were assessed for association with 1091 cardiovascular deaths or non-fatal myocardial infarction (MI). Risk factors were age over 65 years, male gender [hazard ratio (HR) 1.2], previous MI (HR 1.5), previous stroke and/or peripheral vascular disease (HR 1.7), diabetes, smoking, angina (all HR 1.5), and high serum cholesterol and systolic blood pressure. Treatment benefit by perindopril was consistent among high, intermediate, and low risk patients (HRs 0.88, 0.68, and 0.83, respectively). Risk reduction was thus not modified by absolute risk level. CONCLUSION: Risk factors such as age, male gender, smoking, total cholesterol, and blood pressure continue to play an important role once clinical sequellae of coronary heart disease have developed. Patients at moderate-to-high risk because of uncontrolled risk factors and those with other indications for ACE-inhibitors have the most to gain from ACE-inhibition.

Hou, F. F., X. Zhang, et al. (2006). "Efficacy and safety of benazepril for advanced chronic renal insufficiency.[see comment]." New England Journal of Medicine **354**(2): 131-40.

BACKGROUND: Angiotensin-converting-enzyme inhibitors provide renal protection in patients with mild-to-moderate renal insufficiency (serum creatinine level, 3.0 mg per deciliter or less). We assessed the efficacy and safety of benazepril in patients without diabetes who had advanced renal insufficiency. METHODS: We enrolled 422 patients in a randomized, double-blind study. After an eight-week run-in period, 104 patients with serum creatinine levels of 1.5 to 3.0 mg per deciliter (group 1) received 20 mg of benazepril per day, whereas 224 patients with serum creatinine levels of 3.1 to 5.0 mg per deciliter (group 2) were randomly assigned to receive 20 mg of benazepril per day (112 patients) or placebo (112 patients) and then followed for a mean of 3.4 years. All patients received conventional antihypertensive therapy. The primary outcome was the composite of a doubling of the serum creatinine level, end-stage renal disease, or death. Secondary end points included changes in the level of proteinuria and the rate of progression of renal disease. RESULTS: Of 102 patients in group 1, 22 (22 percent) reached the primary end point, as compared with 44 of 108 patients given benazepril in group 2 (41 percent) and 65 of 107 patients given placebo in group 2 (60 percent). As compared with placebo, benazepril was associated with a 43 percent reduction in the risk of the primary end point

in group 2 (P=0.005). This benefit did not appear to be attributable to blood-pressure control. Benazepril therapy was associated with a 52 percent reduction in the level of proteinuria and a reduction of 23 percent in the rate of decline in renal function. The overall incidence of major adverse events in the benazepril and placebo subgroups of group 2 was similar. CONCLUSIONS: Benazepril conferred substantial renal benefits in patients without diabetes who had advanced renal insufficiency. (ClinicalTrials.gov number, NCT00270426.) Copyright 2006 Massachusetts Medical Society.

Investigators, D. T., J. Bosch, et al. (2006). "Effect of ramipril on the incidence of diabetes.[see comment]." New England Journal of Medicine **355**(15): 1551-62.

BACKGROUND: Previous studies have suggested that blockade of the renin-angiotensin system may prevent diabetes in people with cardiovascular disease or hypertension. METHODS: In a double-blind, randomized clinical trial with a 2-by-2 factorial design, we randomly assigned 5269 participants without cardiovascular disease but with impaired fasting glucose levels (after an 8-hour fast) or impaired glucose tolerance to receive ramipril (up to 15 mg per day) or placebo (and rosiglitazone or placebo) and followed them for a median of 3 years. We studied the effects of ramipril on the development of diabetes or death, whichever came first (the primary outcome), and on secondary outcomes, including regression to normoglycemia. RESULTS: The incidence of the primary outcome did not differ significantly between the ramipril group (18.1%) and the placebo group (19.5%; hazard ratio for the ramipril group, 0.91; 95% confidence interval [CI], 0.81 to 1.03; P=0.15). Participants receiving ramipril were more likely to have regression to normoglycemia than those receiving placebo (hazard ratio, 1.16; 95% CI, 1.07 to 1.27; P=0.001). At the end of the study, the median fasting plasma glucose level was not significantly lower in the ramipril group (102.7 mg per deciliter [5.70 mmol per liter]) than in the placebo group (103.4 mg per deciliter [5.74 mmol per liter], P=0.07), though plasma glucose levels 2 hours after an oral glucose load were significantly lower in the ramipril group (135.1 mg per deciliter [7.50 mmol per liter] vs. 140.5 mg per deciliter [7.80 mmol per liter], P=0.01). CONCLUSIONS: Among persons with impaired fasting glucose levels or impaired glucose tolerance, the use of ramipril for 3 years does not significantly reduce the incidence of diabetes or death but does significantly increase regression to normoglycemia. (ClinicalTrials.gov number, NCT00095654 [ClinicalTrials.gov].). Copyright 2006 Massachusetts Medical Society.

Konstam, M. A., J. D. Neaton, et al. (2005). "Comparison of losartan and captopril on heart failure-related outcomes and symptoms from the losartan heart failure survival study (ELITE II)." American Heart Journal **150**(1): 123-31.

BACKGROUND: Blockade of the renin-angiotensin system with angiotensin-converting enzyme inhibitors improves outcomes and symptoms in patients with heart failure (HF). We compared effects of losartan to captopril on mortality, morbidity, and functional status for patients in the ELITE II study. METHODS AND RESULTS: A total of 3152 patients, aged 60 years or older, with New York Heart Association (NYHA) classes II to IV HF and ejection fraction < or = 40% were assigned to receive losartan 50 mg once daily or captopril 50 mg 3 times daily. Outcome measures included all-cause and HF-related mortality, hospitalizations, and discontinuations; change in NYHA class; and quality of life (QoL). HF-related outcomes were not significantly different between therapies. Similar improvements from baseline (P < .01) in NYHA class were observed

within both treatment groups. Among 1856 QoL participants, 1343 patients survived at least 1 year; the QoL for 1-year survivors improved in both treatment groups (P < .001 vs baseline) and did not differ between groups. CONCLUSIONS: In ELITE II, the effects of losartan on HF-related outcomes, NYHA class, and QoL were not superior to those of captopril. Although angiotensin-converting enzyme inhibitors remain the treatment of choice for patients with HF, the similarity of the findings in the present analysis supports a role for angiotensin-receptor antagonists in this patient population.

Kostis, J. B., H. J. Kim, et al. (2005). "Incidence and characteristics of angioedema associated with enalapril." Archives of Internal Medicine **165**(14): 1637-42.

BACKGROUND: Angioedema is a rare but potentially serious adverse event of angiotensin-converting enzyme inhibitor therapy. However, no prospective, controlled studies have reported on its incidence and clinical characteristics. METHODS: We studied the occurrence of angioedema in a randomized, double-blind, controlled trial of 12 557 persons with hypertension treated with enalapril maleate, 5 to 40 mg/d, using a prospective ascertainment and adjudication of angioedema by an expert committee. RESULTS: Angioedema occurred in 86 (0.68%) of the subjects. Stepwise logistic regression identified black race (odds ratio [OR], 2.88; 95% confidence interval [CI], 1.72-4.82), history of drug rash (OR, 3.78; 95% CI, 1.80-7.92), age greater than 65 years (OR, 1.60; 95% CI, 1.02-2.53), and seasonal allergies (OR, 1.79; 95% CI, 1.06-3.00) as independent risk factors for angioedema. The incidence of angioedema was higher after initiation of therapy (3.6/1000 patients per month) and declined to 0.4/1000 patients per month. Treatment was not given in 44 (51%) of the cases; antihistamines were administered in 35 (41%); corticosteroids, in 20 (23%); and epinephrine, in 1 (1%). Two patients were hospitalized but none had airway compromise. CONCLUSIONS: Enalapril-related angioedema is uncommon. Although it is most likely to occur early after initiation of therapy, it may occur at any time. It is more likely to occur in black patients, those older than 65 years, and those with a history of drug rash or seasonal allergies. Fatal angioedema or angioedema requiring airway protection did not occur in this study.

Lash, J. P., X. Wang, et al. (2006). "Quality of life in the African American Study of Kidney Disease and Hypertension: effects of blood pressure management." American Journal of Kidney Diseases **47**(6): 956-64.

BACKGROUND: The African American Study of Kidney Disease and Hypertension was a multicenter trial comparing the effects of 2 levels of blood pressure control (usual or low goal) and initial therapy with metoprolol, ramipril, or amlodipine. We examined effects of treatment-group assignment on health-related quality of life (HRQOL) measures and reported symptoms during 4 years of follow-up. METHODS: HRQOL was assessed at baseline and annually by using the Medical Outcomes Study 36-Item Short Form (SF-36) and a symptom checklist. Using a 2-slope model, treatment effects were evaluated for change from baseline to year 1 and for average change during the first 4 years of follow-up. RESULTS: A total of 1,094 participants were randomly assigned. Average age was 55 years, 61% were men, and the mean of the first glomerular filtration rate in the study was 46 mL/min/1.73 m2 (0.76 mL/s). No significant differences in HRQOL were seen between the low- and usual-blood-pressure groups. Reported side effects also were similar between blood-pressure groups. Mean Physical Health Component (PHC) and Mental Health Component (MHC) scores had a significantly

smaller decrease in the ramipril than metoprolol group in both the initial period from baseline to year 1 (PHC, 2.08 +/- 0.56; MHC, 1.89 +/- 0.62) and during the first 4 years of follow-up (PHC, 1.60 +/- 0.44; MHC, 1.48 +/- 0.48). The MHC also had a slightly smaller decrease during the first 4 years in the ramipril group than amlodipine group (1.20 +/- 0.61). CONCLUSION: Aggressive blood pressure control is well tolerated in African Americans with hypertensive kidney disease, measured by using the SF-36 and reported symptoms. The clinical significance of smaller decreases in PHC and MHC scores in the ramipril compared with metoprolol group is not clear.

Leenen, F. H. H., C. E. Nwachuku, et al. (2006). "Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the antihypertensive and lipid-lowering treatment to prevent heart attack trial.[see comment]." Hypertension **48**(3): 374-84.

The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) provides a unique opportunity to compare the long-term relative safety and efficacy of angiotensin-converting enzyme inhibitor and calcium channel blocker-initiated therapy in older hypertensive individuals. Patients were randomized to amlodipine (n=9048) or lisinopril (n=9054). The primary outcome was combined fatal coronary heart disease or nonfatal myocardial infarction, analyzed by intention-to-treat. Secondary outcomes included all-cause mortality, stroke, combined cardiovascular disease (CVD), end-stage renal disease (ESRD), cancer, and gastrointestinal bleeding. Mean follow-up was 4.9 years. Blood pressure control was similar in nonblacks, but not in blacks. No significant differences were found between treatment groups for the primary outcome, all-cause mortality, ESRD, or cancer. Stroke rates were higher on lisinopril in blacks (RR=1.51, 95% CI 1.22 to 1.86) but not in nonblacks (RR=1.07, 95% CI 0.89 to 1.28), and in women (RR=1.45, 95% CI 1.17 to 1.79), but not in men (RR=1.10, 95% CI 0.92 to 1.31). Rates of combined CVD were higher (RR=1.06, 95% CI 1.00 to 1.12) because of higher rates for strokes, peripheral arterial disease, and angina, which were partly offset by lower rates for heart failure (RR=0.87, 95% CI 0.78 to 0.96) on lisinopril compared with amlodipine. Gastrointestinal bleeds and angioedema were higher on lisinopril. Patients with and without baseline coronary heart disease showed similar outcome patterns. We conclude that in hypertensive patients, the risks for coronary events are similar, but for stroke, combined CVD, gastrointestinal bleeding, and angioedema are higher and for heart failure are lower for lisinopril-based compared with amlodipine-based therapy. Some, but not all, of these differences may be explained by less effective blood pressure control in the lisinopril arm.

MacGregor, M. S., C. J. Deighan, et al. (2005). "A prospective open-label randomised trial of quinapril and/or amlodipine in progressive non-diabetic renal failure." Nephron **101**(3): c139-49.

BACKGROUND: Treatment of hypertension slows the progression of non-diabetic nephropathies, but the optimal regimen is unknown. Angiotensin-converting enzyme inhibitors are more effective than beta-blockers, but their merits relative to calcium channel blockers are less clear. METHODS: 73 hypertensive patients with progressive non-diabetic nephropathies were prospectively randomised to open-label quinapril (Q, n = 28), amlodipine (A, n = 28) or both drugs (Q&A, n = 17). Therapy was increased to achieve a diastolic blood pressure < 90 mm Hg. Patients were followed for 4 years or until death. The primary outcome was the combined endpoint of doubling serum

creatinine, starting renal replacement therapy or death. RESULTS: There was no significant difference in the primary outcome, or in the change of glomerular filtration rate. Blood pressure was equally controlled throughout the study period. 29 (40%) patients were withdrawn from the allocated therapy (Q 39%, A 36%, Q&A 47%). Because of the large crossover between trial arms, the data were re-analysed per protocol. The effect on preventing the need for renal replacement therapy then approached significance between the groups (p = 0.089) and the combined quinapril-containing groups were less likely than the amlodipine group to achieve the primary endpoint (p = 0.038), or the individual endpoints of renal replacement therapy (p = 0.030) or doubling creatinine (p = 0.051). CONCLUSIONS: Quinapril is more effective than amlodipine at reducing the incidence of dialysis in patients with progressive renal failure, but only if they can tolerate the drug. The tolerability of these drugs in patients with advanced renal failure is poor. Copyright 2005 S. Karger AG, Basel.

Norris, K., J. Bourgoigne, et al. (2006). "Cardiovascular outcomes in the African American Study of Kidney Disease and Hypertension (AASK) Trial." American Journal of Kidney Diseases **48**(5): 739-51.

BACKGROUND: Patients with chronic kidney disease are at increased risk for cardiovascular (CV) events. METHODS: We randomly assigned 1,094 African Americans with hypertensive nephrosclerosis (glomerular filtration rate [GFR], 20 to 65 mL/min/1.73 m(2) [0.33 to 1.08 mL/s]) to initial antihypertensive treatment with either: (1) a beta-blocker, metoprolol; (2) an angiotensin-converting enzyme inhibitor, ramipril; or (3) a dihydropyridine calcium channel blocker, amlodipine, and either a usual-blood pressure (BP) or low-BP treatment goal. Using a design powered to detect renal outcome differences, we compared the effect of treatment on the CV event rate (cardiac death, myocardial infarction, stroke, and heart failure) during a mean follow-up period of 4.1 years and determined baseline factors that predict CV outcomes. RESULTS: Thirty-one patients died of CV disease (0.7%/patient-year), and 149 patients experienced at least 1 CV outcome (3.3%/patient-year). Overall, 202 CV events (4.5%/patient-year) occurred. The CV outcome rate was not related significantly to randomized interventions. In multivariable analyses, 7 baseline risk factors remained independently associated with increased risk for the CV composite outcome after controlling for age, sex, baseline GFR, and baseline proteinuria group: pulse pressure, duration of hypertension, abnormal electrocardiogram result, non-high-density lipoprotein cholesterol level, serum urea nitrogen level, urine protein-creatinine ratio, urine sodium-potassium ratio, and annual income less than 15,000 dollars. CONCLUSION: Neither randomized class of antihypertensive therapy nor BP level had a significant effect on the occurrence of CV events, possibly because of limited power. However, this analysis identifies unique and potentially modifiable CV risk factors in this high-risk cohort.

Piller, L. B., C. E. Ford, et al. (2006). "Incidence and predictors of angioedema in elderly hypertensive patients at high risk for cardiovascular disease: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)." Journal of Clinical Hypertension **8**(9): 649-56; quiz 657-8.

Angioedema is a rare, potentially life-threatening condition that has been associated with angiotensin-converting enzyme inhibitors since their introduction in the 1980s. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

(ALLHAT), the largest antihypertensive study conducted to date, randomized 42,418 participants to a diuretic (chlorthalidone), a calcium channel blocker (amlodipine), an angiotensin-converting enzyme inhibitor (lisinopril), or an alpha-blocker (doxazosin). Patients who developed angioedema were compared for baseline characteristics and changes in antihypertensive drug administration. Fifty-three participants developed angioedema during active follow-up: 55% were black, 60% men, and 70% were assigned to lisinopril (including 62% of black participants with angioedema), 15% to chlorthalidone, 9% to doxazosin, and 6% to amlodipine. Six percent occurred within a day of randomization and 23% within the first week. Over half did not have an increase in their assigned (blinded) antihypertensive drug before angioedema onset; 3 (6%) had a dose increase within a week before onset. One patient died following an angioedema episode. The occurrence of angioedema in the angiotensin-converting enzyme inhibitor arm corresponds with previously reported angioedema-angiotensin-converting enzyme inhibitor associations.

Rahman, M., S. Pressel, et al. (2005). "Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[see comment]." Archives of Internal Medicine **165**(8): 936-46.

BACKGROUND: This study was performed to determine whether, in high-risk hypertensive patients with a reduced glomerular filtration rate (GFR), treatment with a calcium channel blocker or an angiotensin-converting enzyme inhibitor lowers the incidence of renal disease outcomes compared with treatment with a diuretic. METHODS: We conducted post hoc analyses of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Hypertensive participants 55 years or older with at least 1 other coronary heart disease risk factor were randomized to receive chlorthalidone, amlodipine, or lisinopril for a mean of 4.9 years. Renal outcomes were incidence of end-stage renal disease (ESRD) and/or a decrement in GFR of 50% or more from baseline. Baseline GFR, estimated by the simplified Modification of Diet in Renal Disease equation, was stratified into normal or increased (> or =90 mL /min per 1.73 m(2), n = 8126), mild reduction (60-89 mL /min per 1.73 m(2), n = 18 109), or moderate-severe reduction (<60 mL /min per 1.73 m(2), n = 5662) in GFR. Each stratum was analyzed for effects of the treatments on outcomes. RESULTS: In 448 participants, ESRD developed. Compared with patients taking chlorthalidone, no significant differences occurred in the incidence of ESRD in patients taking amlodipine in the mild (relative risk [RR], 1.47; 95% confidence interval [CI], 0.97-2.23) or moderate-severe (RR, 0.92; 95% CI, 0.68-1.24) reduction in GFR groups. Compared with patients taking chlorthalidone, no significant differences occurred in the incidence of ESRD in patients taking lisinopril in the mild (RR, 1.34; 95% CI, 0.87-2.06) or moderate-severe (RR, 0.98; 95% CI, 0.73-1.31) reduction in GFR groups. In patients with mild and moderate-severe reduction in GFR, the incidence of ESRD or 50% or greater decrement in GFR was not significantly different in patients treated with chlorthalidone compared with those treated with amlodipine (odds ratios, 0.96 [P = .74] and 0.85 [P = .23], respectively) and lisinopril (odds ratios, 1.13 [P = .31] and 1.00 [P = .98], respectively). No difference in treatment effects occurred for either end point for patients taking amlodipine or lisinopril compared with those taking chlorthalidone across the 3 GFR subgroups, either for the total group or for participants with diabetes at baseline. At 4

years of follow-up, estimated GFR was 3 to 6 mL /min per 1.73 m(2) higher in patients assigned to receive amlodipine compared with chlorthalidone, depending on baseline GFR stratum. CONCLUSIONS: In hypertensive patients with reduced GFR, neither amlodipine nor lisinopril was superior to chlorthalidone in reducing the rate of development of ESRD or a 50% or greater decrement in GFR. Participants assigned to receive amlodipine had a higher GFR than those assigned to receive chlorthalidone, but rates of development of ESRD were not different between the groups.

Rahman, M., S. Pressel, et al. (2006). "Cardiovascular outcomes in high-risk hypertensive patients stratified by baseline glomerular filtration rate.[see comment][summary for patients in Ann Intern Med. 2006 Feb 7;144(3):I33; PMID: 16461958]." Annals of Internal Medicine **144**(3): 172-80.

BACKGROUND: Chronic kidney disease is common in older patients with hypertension. OBJECTIVE: To compare rates of coronary heart disease (CHD) and end-stage renal disease (ESRD) events; to determine whether glomerular filtration rate (GFR) independently predicts risk for CHD; and to report the efficacy of first-step treatment with a calcium-channel blocker (amlodipine) or an angiotensin-converting enzyme inhibitor (lisinopril), each compared with a diuretic (chlorthalidone), in modifying cardiovascular disease (CVD) outcomes in high-risk patients with hypertension stratified by GFR. DESIGN: Post hoc subgroup analysis. SETTING: Multicenter randomized, double-blind, controlled trial. PARTICIPANTS: Persons with hypertension who were 55 years of age or older with 1 or more risk factors for CHD and who were stratified into 3 baseline GFR groups: normal or increased (> or = 90 mL/min per 1.73 m2; n = 8126 patients), mild reduction (60 to 89 mL/min per 1.73 m2; n = 18,109 patients), and moderate or severe reduction (< 60 mL/min per 1.73 m2; n = 5662 patients). INTERVENTIONS: Random assignment to chlorthalidone, amlodipine, or lisinopril. MEASUREMENTS: Rates of ESRD, CHD, stroke, and combined CVD (CHD, coronary revascularization, angina, stroke, heart failure, and peripheral arterial disease). RESULTS: In participants with a moderate to severe reduction in GFR, 6-year rates were higher for CHD than for ESRD (15.4% vs. 6.0%, respectively). A baseline GFR of less than 53 mL/min per 1.73 m2 (compared with >104 mL/min per 1.73 m2) was independently associated with a 32% higher risk for CHD. Amlodipine was similar to chlorthalidone in reducing CHD (16.0% vs. 15.2%, respectively; hazard ratio, 1.06 [95% CI, 0.89 to 1.27]), stroke, and combined CVD (CHD, coronary revascularization, angina, stroke, heart failure, and peripheral arterial disease), but less effective in preventing heart failure. Lisinopril was similar to chlorthalidone in preventing CHD (15.1% vs. 15.2%, respectively; hazard ratio, 1.00 [CI, 0.84 to 1.20]), but was less effective in reducing stroke, combined CVD events, and heart failure. LIMITATIONS: Proteinuria data were not available, and combination therapies were not tested. CONCLUSIONS: Older high-risk patients with hypertension and reduced GFR are more likely to develop CHD than to develop ESRD. A low GFR independently predicts increased risk for CHD. Neither amlodipine nor lisinopril is superior to chlorthalidone in preventing CHD, stroke, or combined CVD, and chlorthalidone is superior to both for preventing heart failure, independent of level of renal function.

Solomon, S. D., M. M. Rice, et al. (2006). "Renal function and effectiveness of angiotensin-converting enzyme inhibitor therapy in patients with chronic stable coronary disease in the

Prevention of Events with ACE inhibition (PEACE) trial.[see comment]." Circulation **114**(1): 26-31.

BACKGROUND: Patients with reduced renal function are at increased risk for adverse cardiovascular outcomes. In the post-myocardial infarction setting, angiotensin-converting enzyme (ACE) inhibitors have been shown to be as effective in patients with impaired renal function as in those with preserved renal function. METHODS AND RESULTS: We assessed the relation between renal function and outcomes, the influence of ACE inhibition on this relation, and whether renal function modifies the effectiveness of ACE inhibition in patients with stable coronary artery disease and preserved systolic function enrolled in the Prevention of Events with ACE inhibition trial (PEACE). Patients (n=8290) were randomly assigned to receive trandolapril (target, 4 mg/d) or placebo. Clinical creatinine measures were available for 8280 patients before randomization. The estimated glomerular filtration rate (eGFR) was calculated with the 4-point Modification of Diet in Renal Disease equation. Renal function was related to outcomes, and the influence of ACE-inhibitor therapy was assessed with formal interaction modeling. The mean eGFR in PEACE was 77.6+/-19.4, and 1355 (16.3%) patients had reduced renal function (eGFR <60 mg.mL(-1).1.73 m(-2)). We observed a significant interaction between eGFR and treatment group with respect to cardiovascular and all-cause mortality (P=0.02). Trandolapril was associated with a reduction in total mortality in patients with reduced renal function (adjusted HR, 0.73; 95% CI, 0.54 to 1.00) but not in patients with preserved renal function (adjusted HR, 0.94; 95% CI, 0.78 to 1.13). CONCLUSIONS: Although trandolapril did not improve survival in the overall PEACE cohort, in which mean eGFR was relatively high, trandolapril reduced mortality in patients with reduced eGFR. These data suggest that reduced renal function may define a subset of patients most likely to benefit from ACE-inhibitor therapy for cardiovascular protection.

Whelton, P. K., J. Barzilay, et al. (2005). "Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[see comment]." Archives of Internal Medicine **165**(12): 1401-9.

BACKGROUND: Optimal first-step antihypertensive drug therapy in type 2 diabetes mellitus (DM) or impaired fasting glucose levels (IFG) is uncertain. We wished to determine whether treatment with a calcium channel blocker or an angiotensin-converting enzyme inhibitor decreases clinical complications compared with treatment with a thiazide-type diuretic in DM, IFG, and normoglycemia (NG). METHODS: Active-controlled trial in 31 512 adults, 55 years or older, with hypertension and at least 1 other risk factor for coronary heart disease, stratified into DM (n = 13 101), IFG (n = 1399), and NG (n = 17 012) groups on the basis of national guidelines. Participants were randomly assigned to double-blind first-step treatment with chlorthalidone, 12.5 to 25 mg/d, amlodipine besylate, 2.5 to 10 mg/d, or lisinopril, 10 to 40 mg/d. We conducted an intention-to-treat analysis of fatal coronary heart disease or nonfatal myocardial infarction (primary outcome), total mortality, and other clinical complications. RESULTS: There was no significant difference in relative risk (RR) for the primary outcome in DM or NG participants assigned to amlodipine or lisinopril vs chlorthalidone or in IFG participants assigned to lisinopril vs chlorthalidone. A significantly higher RR (95% confidence interval) was noted for the primary outcome in IFG participants

assigned to amlodipine vs chlorthalidone (1.73 [1.10-2.72]). Stroke was more common in NG participants assigned to lisinopril vs chlorthalidone (1.31 [1.10-1.57]). Heart failure was more common in DM and NG participants assigned to amlodipine (1.39 [1.22-1.59] and 1.30 [1.12-1.51], respectively) or lisinopril (1.15 [1.00-1.32] and 1.19 [1.02-1.39], respectively) vs chlorthalidone. CONCLUSION: Our results provide no evidence of superiority for treatment with calcium channel blockers or angiotensin-converting enzyme inhibitors compared with a thiazide-type diuretic during first-step antihypertensive therapy in DM, IFG, or NG.

White, H. D., P. E. G. Aylward, et al. (2005). "Mortality and morbidity remain high despite captopril and/or Valsartan therapy in elderly patients with left ventricular systolic dysfunction, heart failure, or both after acute myocardial infarction: results from the Valsartan in Acute Myocardial Infarction Trial (VALIANT)." Circulation **112**(22): 3391-9.

BACKGROUND: The elderly constitute an increasing proportion of acute myocardial infarction patients and have disproportionately high mortality and morbidity. Those with heart failure or impaired left ventricular left ventricular function after acute myocardial infarction have high complication and mortality rates. Little is known about outcomes with contemporary therapies in these patients. METHODS AND RESULTS: The Valsartan in Acute Myocardial Infarction Trial (VALIANT) randomized 14,703 patients with heart failure and/or left ventricular ejection fraction <40% to receive captopril, valsartan, or both. Mortality and a composite end point, including cardiovascular mortality, readmission for heart failure, reinfarction, stroke, and resuscitated cardiac arrest, were compared for the age groups of <65 (n=6988), 65 to 74 (n=4555), 75 to 84 (n=2777), and > or =85 (n=383) years. With increasing age, 3-year mortality almost quadrupled (13.4%, 26.3%, 36.0%, and 52.1%, respectively), composite end-point events more than doubled (25.2%, 41.0%, 52.3%, and 66.8%), and hospital admissions for heart failure almost tripled (12.0%, 23.1%, 31.3%, and 35.4%). Outcomes did not differ between the 3 study treatments in any age group. Adverse events associated with captopril and valsartan were more common in the elderly and in patients receiving combination therapy. With increasing age, use of aspirin, beta-blockers, and statins declined, and use of digoxin, calcium-channel blockers, and non-potassium-sparing diuretics increased. On 3-year multivariable analysis, each 10-year age increase was associated with a hazard ratio of 1.49 (95% CI, 1.426 to 1.557; P<0.0001) for mortality and an odds ratio of 1.38 (95% CI, 1.31 to 1.46; P<0.0001) for readmission with heart failure. CONCLUSIONS: Outcomes remained poor in elderly patients with heart failure and/or impaired left ventricular systolic function after acute myocardial infarction, although most received beta-blockers and all received an ACE inhibitor and/or an angiotensin receptor blocker. Better therapies and increased use of aspirin, beta-blockers, and statins are needed in this important and increasing patient group.

Willenheimer, R., D. J. van Veldhuisen, et al. (2005). "Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III.[see comment]." Circulation **112**(16): 2426-35.

BACKGROUND: In patients with chronic heart failure (CHF), a beta-blocker is generally added to a regimen containing an angiotensin-converting-enzyme (ACE) inhibitor. It is unknown whether beta-blockade as initial therapy may be as useful.

METHODS AND RESULTS: We randomized 1010 patients with mild to moderate CHF and left ventricular ejection fraction < or =35%, who were not receiving ACE inhibitor, beta-blocker, or angiotensin receptor blocker therapy, to open-label monotherapy with either bisoprolol (target dose 10 mg QD; n=505) or enalapril (target dose 10 mg BID; n=505) for 6 months, followed by their combination for 6 to 24 months. The 2 strategies were blindly compared with regard to the combined primary end point of all-cause mortality or hospitalization and with regard to each of these end point components individually. Bisoprolol-first treatment was noninferior to enalapril-first treatment if the upper limit of the 95% confidence interval (CI) for the absolute between-group difference was <5%, corresponding to a hazard ratio (HR) of 1.17. In the intention-to-treat sample, the primary end point occurred in 178 patients allocated to bisoprolol-first treatment versus 186 allocated to enalapril-first treatment (absolute difference -1.6%, 95% CI -7.6 to 4.4%, HR 0.94; 95% CI 0.77 to 1.16). In the per-protocol sample, 163 patients allocated to bisoprolol-first treatment had a primary end point, versus 165 allocated to enalapril-first treatment (absolute difference -0.7%, 95% CI -6.6 to 5.1%, HR 0.97; 95% CI 0.78 to 1.21). With bisoprolol-first treatment, 65 patients died, versus 73 with enalapril-first treatment (HR 0.88; 95% CI 0.63 to 1.22), and 151 versus 157 patients were hospitalized (HR 0.95; 95% CI 0.76 to 1.19). CONCLUSIONS: Although noninferiority of bisoprolol-first versus enalapril-first treatment was not proven in the per-protocol analysis, our results indicate that it may be as safe and efficacious to initiate treatment for CHF with bisoprolol as with enalapril.

Zannad, F., M. Kessler, et al. (2006). "Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of fosinopril and implications for future studies." Kidney International **70**(7): 1318-24.

Cardiovascular events (CVEs) are the leading cause of death in chronic hemodialysis patients. Results of trials in non-end-stage renal disease (ESRD) patients cannot be extrapolated to patients with ESRD. It is critical to test cardiovascular therapies in these high-risk patients who are usually excluded from major cardiovascular trials. The study objective was to evaluate the effect of fosinopril on CVEs in patients with ESRD. Eligible patients were randomized to fosinopril 5 mg titrated to 20 mg daily (n=196) or placebo (n=201) plus conventional therapy for 24 months. The primary end point was combined fatal and nonfatal first major CVEs (cardiovascular death, resuscitated death, nonfatal stroke, heart failure, myocardial infarction, or revascularization). No significant benefit for fosinopril was observed in the intent to treat analysis (n=397) after adjusting for independent predictors of CVEs (RR=0.93, 95% confidence interval (CI) 0.68-1.26, P=0.35). The per protocol secondary supportive analysis (n=380) found a trend towards benefit for fosinopril (adjusted RR=0.79 (95% CI 0.59-1.1, P=0.099)). In the patients who were hypertensive at baseline, systolic and diastolic blood pressures were significantly decreased in the fosinopril as compared to the placebo group. After adjustment for risk factors, trends were observed suggesting fosinopril may be associated with a lower risk of CVEs. These trends may have become statistically significant had the sample size been larger, and these findings warrant further study.